Methotrexate entrained in the hyaluronan meshwork
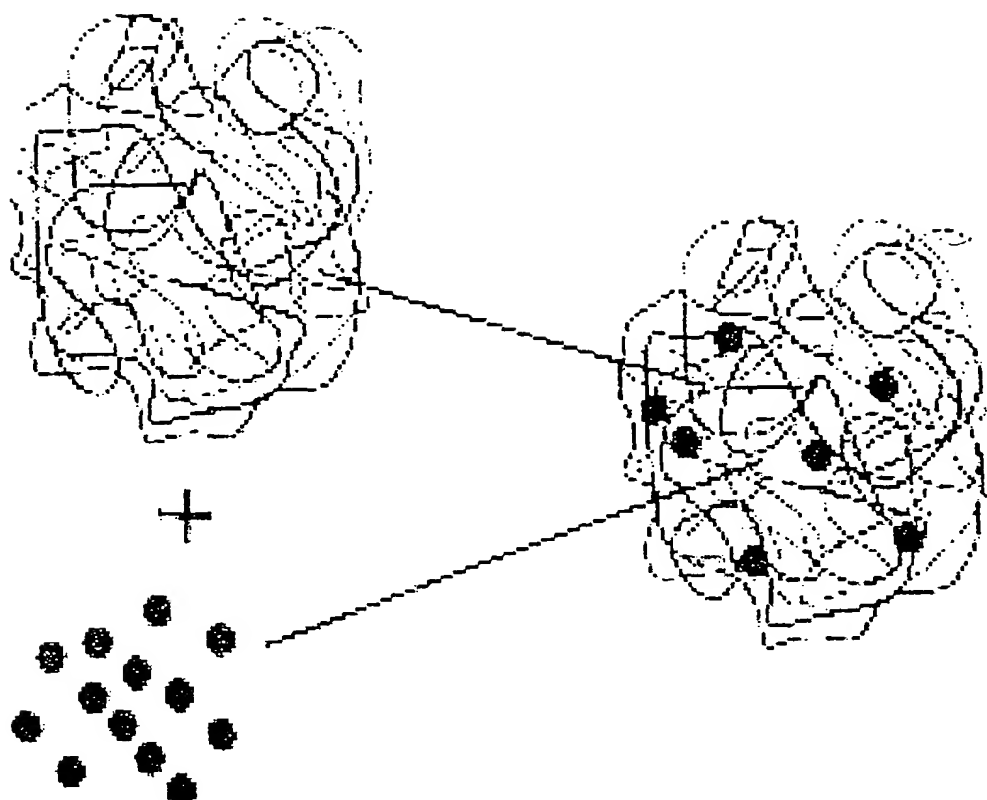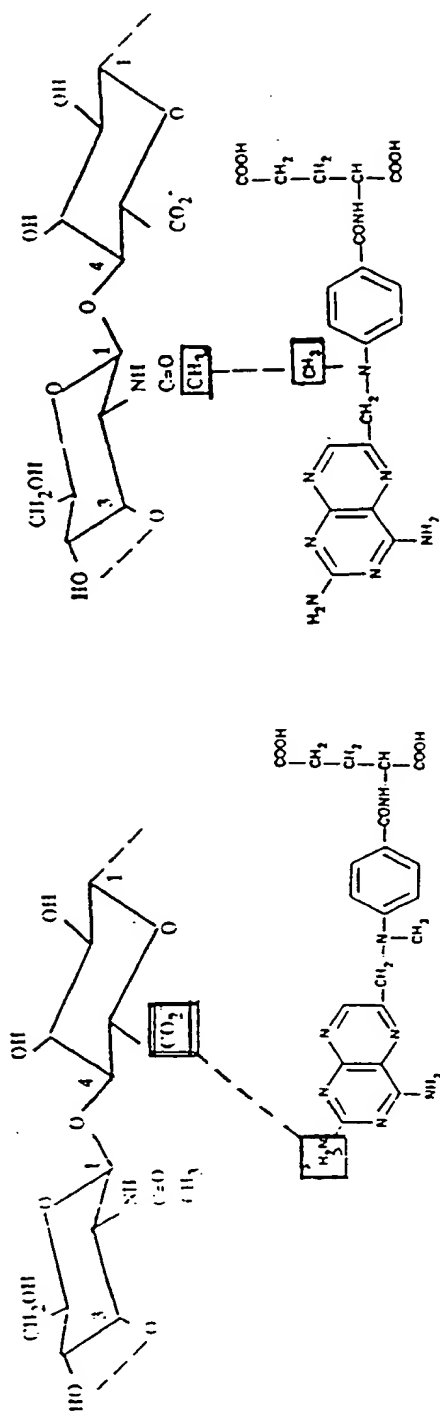

FIGURE 1
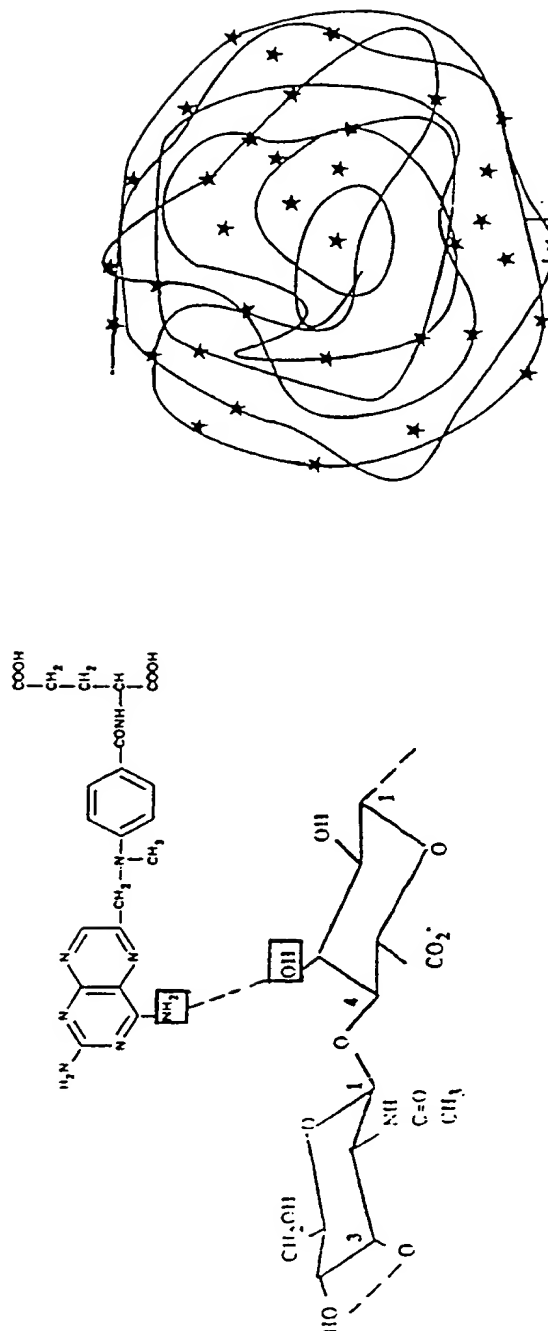
09/889203

A: Possible Interactions Between Methotrexate and Hyaluronan
i: Ionic bonding
ii: Hydrogen bonding
iii: Hydrophobic Bonding

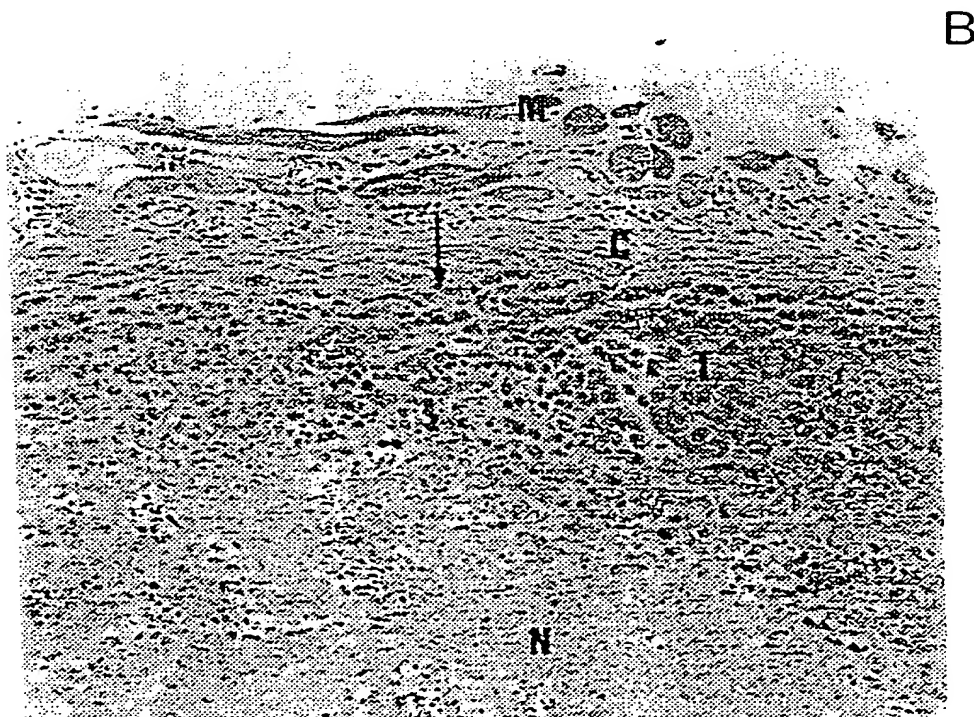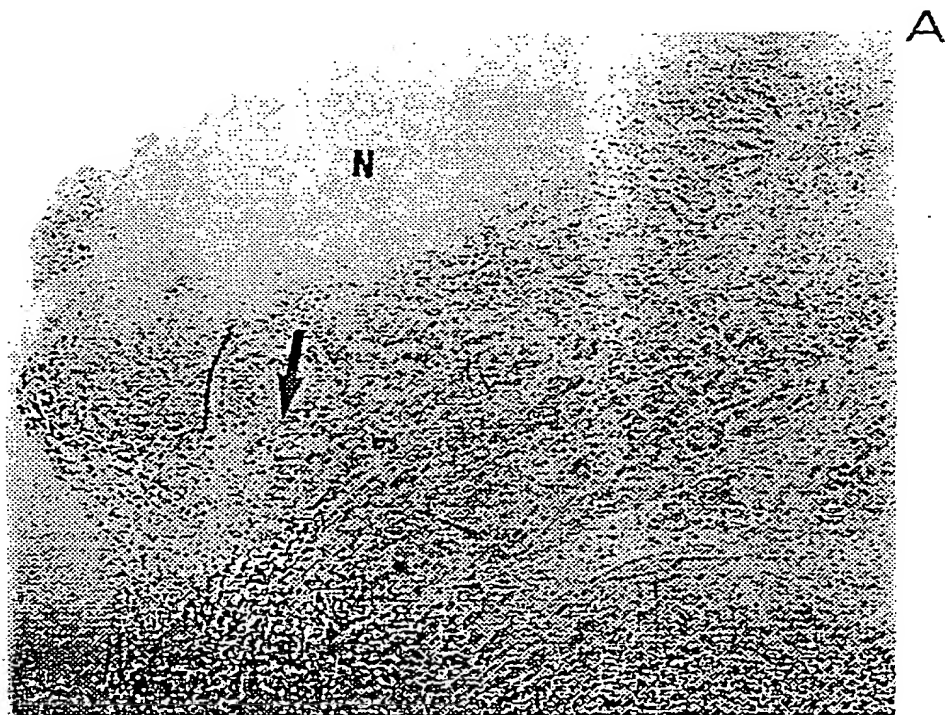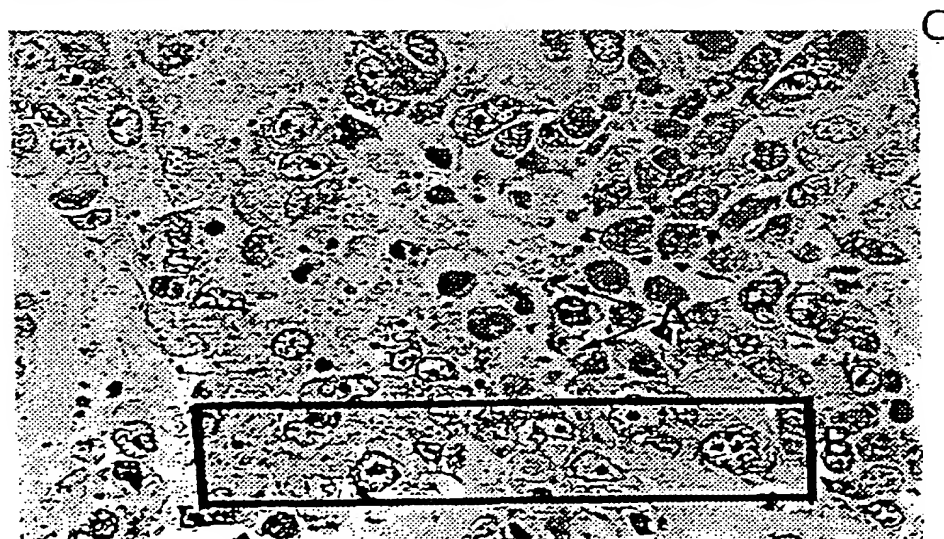B: Entanglement of Methotrexate in Hyaluronan Molecule

FIGURE 2

A

B

FIGURE 3
SUBSTITUTE SHEET (RULE 26) (RO/AU)

FIGURE 4

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FIGURE 5
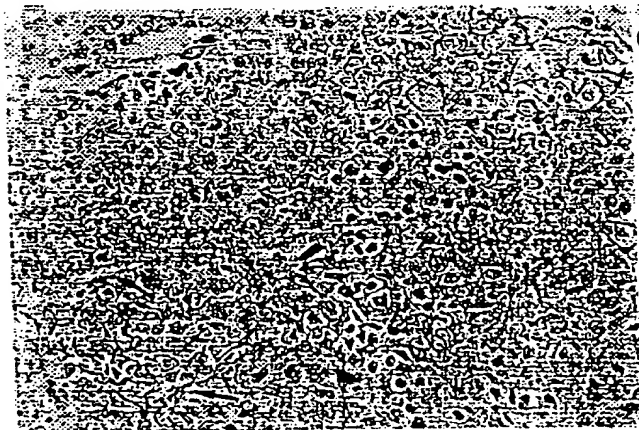
Molecular weight characterisation of hyaluronan
used as a delivery vehicle for methotrexate

FIGURE 6

MTX Uptake by Tumours

HA/MTX
MTX

P=0.021

P=0.050

MTX Dpm (% of injected MTX per g of tumour)

Time after injection (hours)

FIGURE 7

Increased methotrexate uptake by the liver when drug is co-administered with hyaluronan

FIGURE 8

FIGURE 9

Methotrexate

Hyaluronan

Methotrexate becomes
entangled in hyaluronan
meshwork

Hyaluronan carrying
the entrained drug
binds to HA receptors

HA receptor
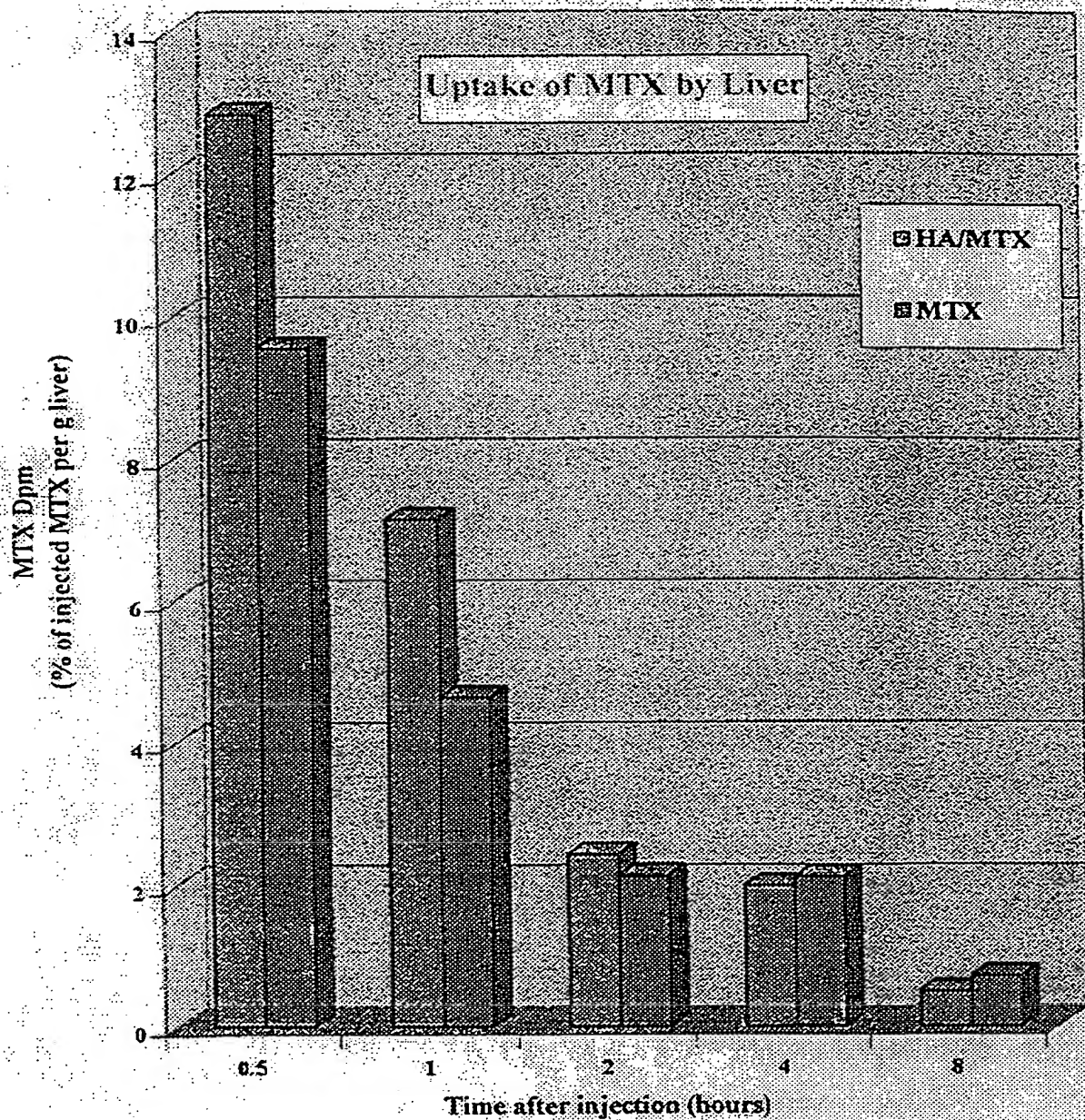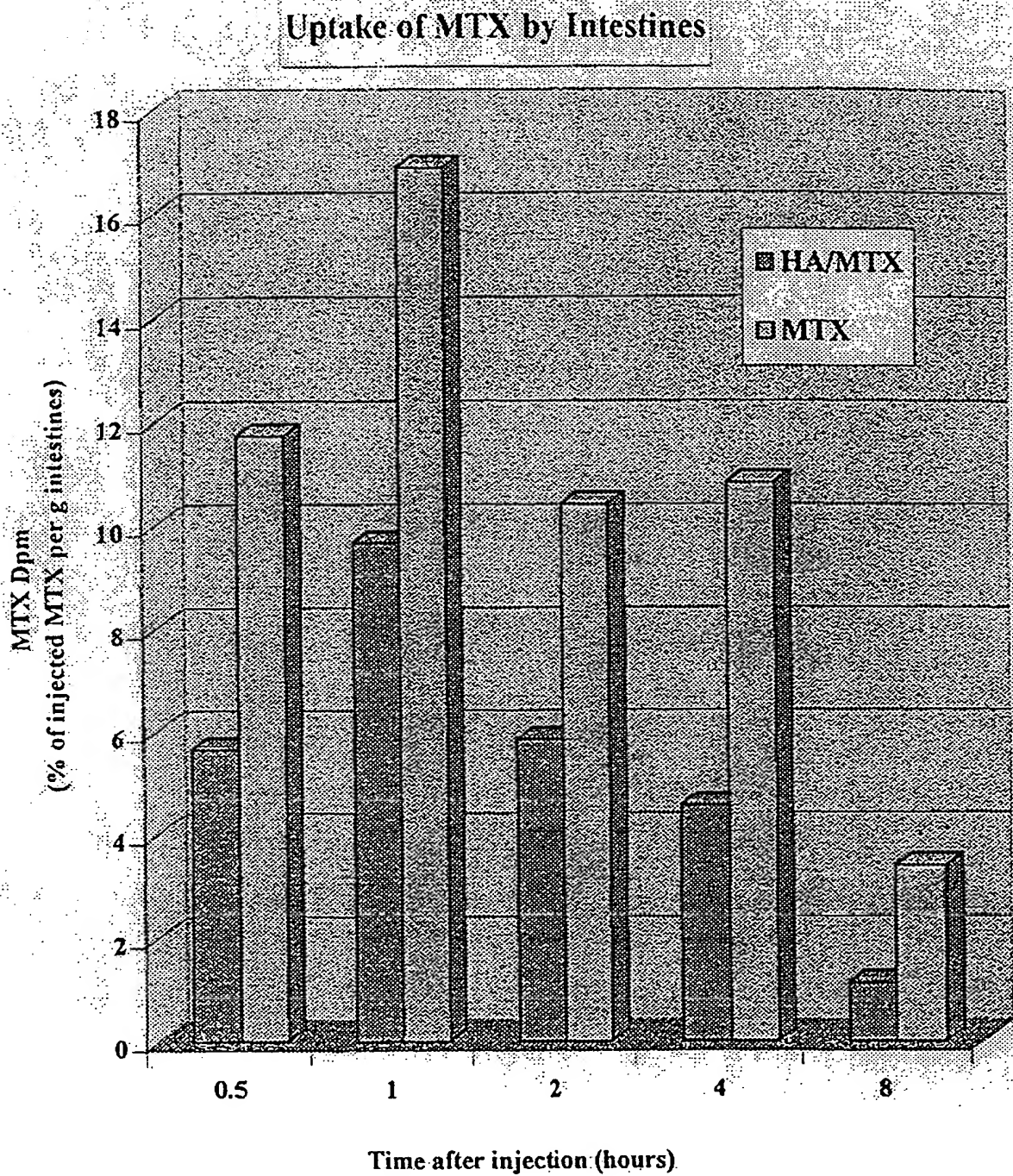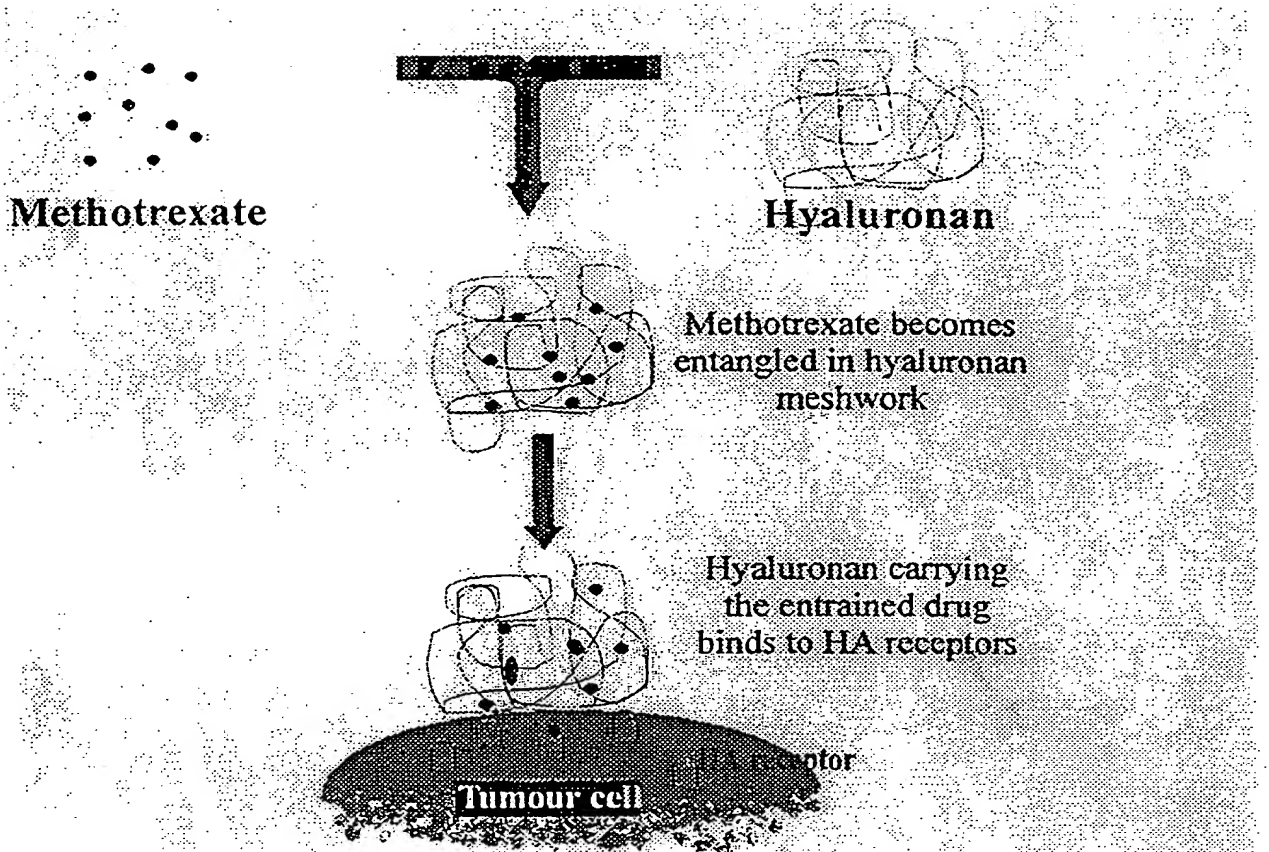
Tumour cell

Two possible mechanisms of drug targeting of tumour cells
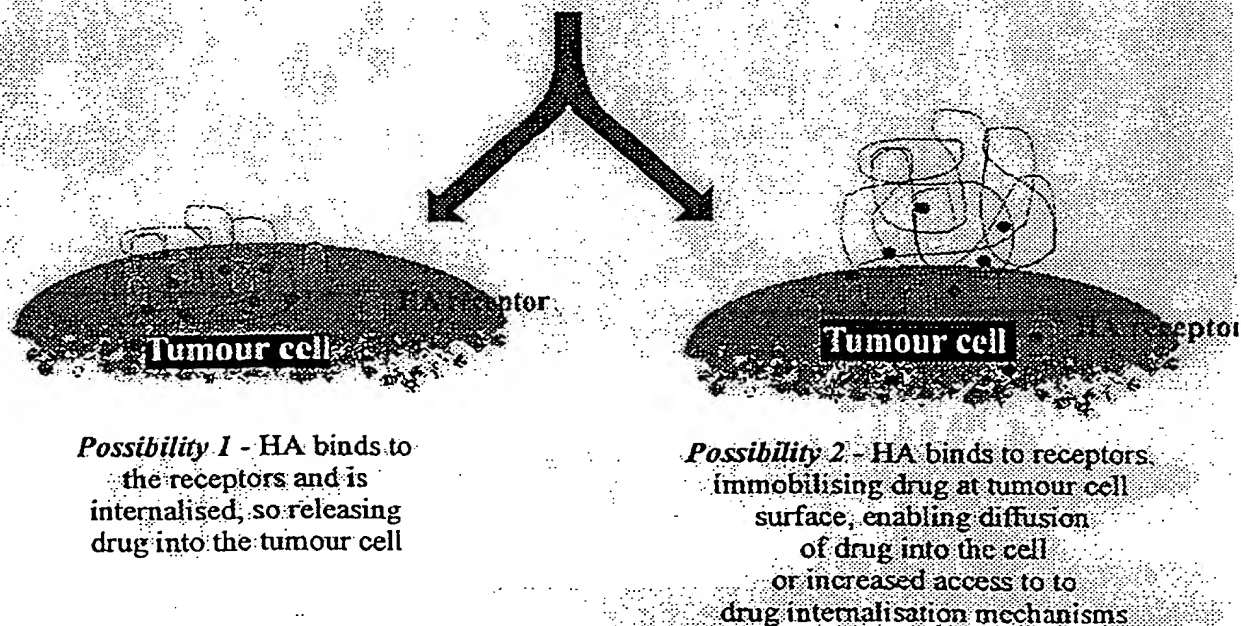
HA receptor

Tumour cell

Tumour cell

receptor

Possibility 1 - HA binds to
the receptors and is
internalised, so releasing
drug into the tumour cell

Possibility 2 - HA binds to receptors,
immobilising drug at tumour cell
surface, enabling diffusion
of drug into the cell
or increased access to to
drug internalisation mechanisms
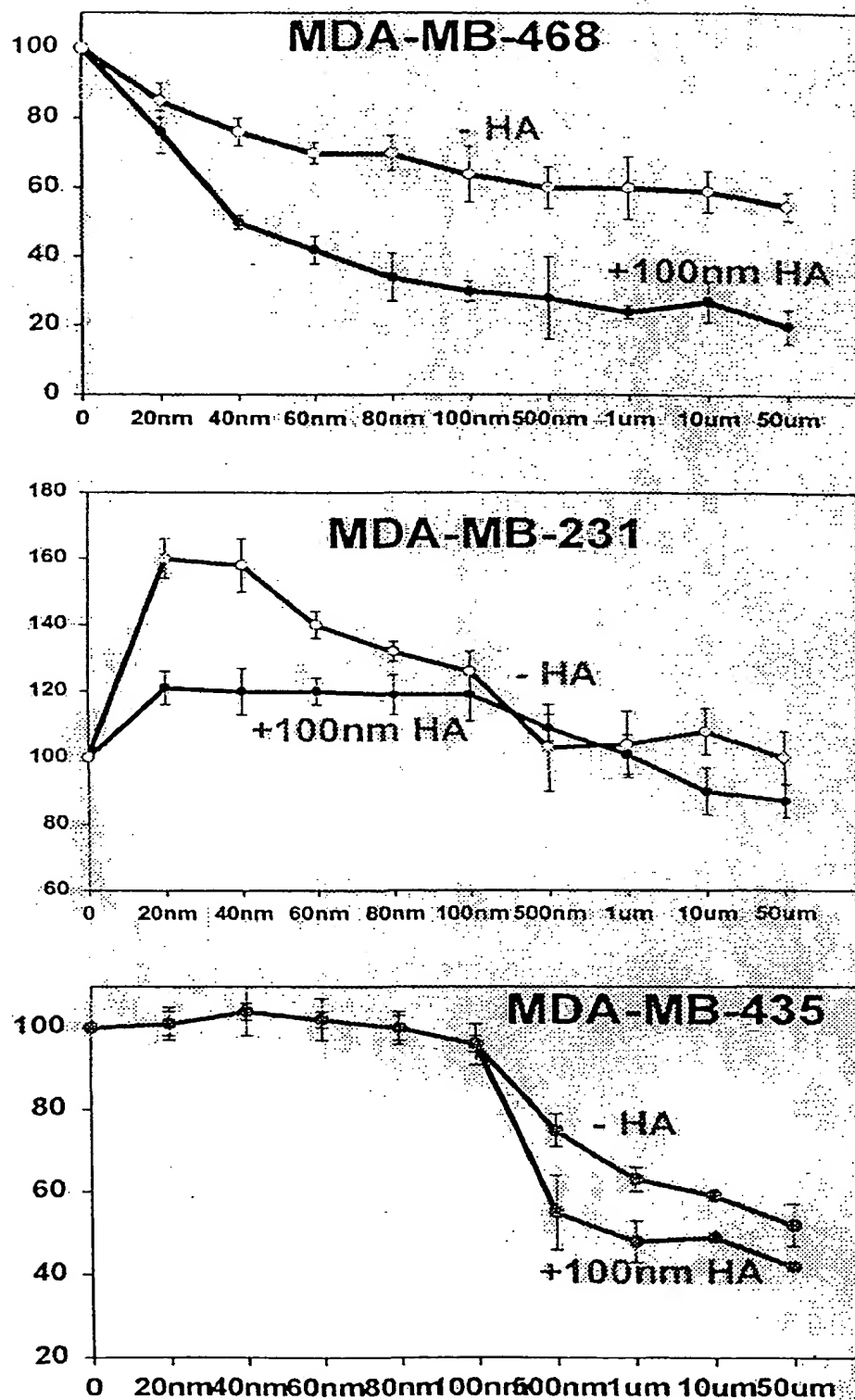
FIGURE 10

FIGURE 11

Tumour Uptake of 5-Fluorouracil
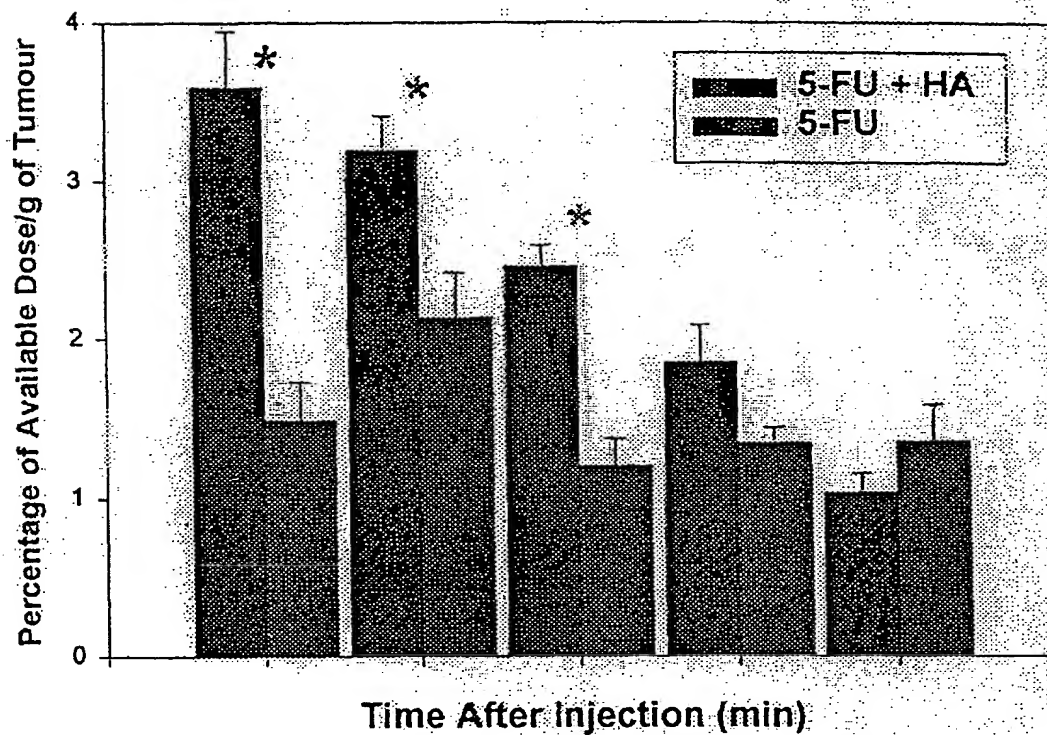
* P= or< 0.001, Students t-test

FIGURE 12

Tissue

33% Local Degradation   67% Escapes into Lymph *

50-90% Metabolised by Lymph Nodes

<17% Reaches Bloodstream

(10-100mg/day delivered to blood)

Plasma

80-90% Metabolised in Liver
(maximum degradation is 350mg/day)

10-15% Excreted via Kidney

0-1% Spleen, etc

Urine
(0.3mg/day)
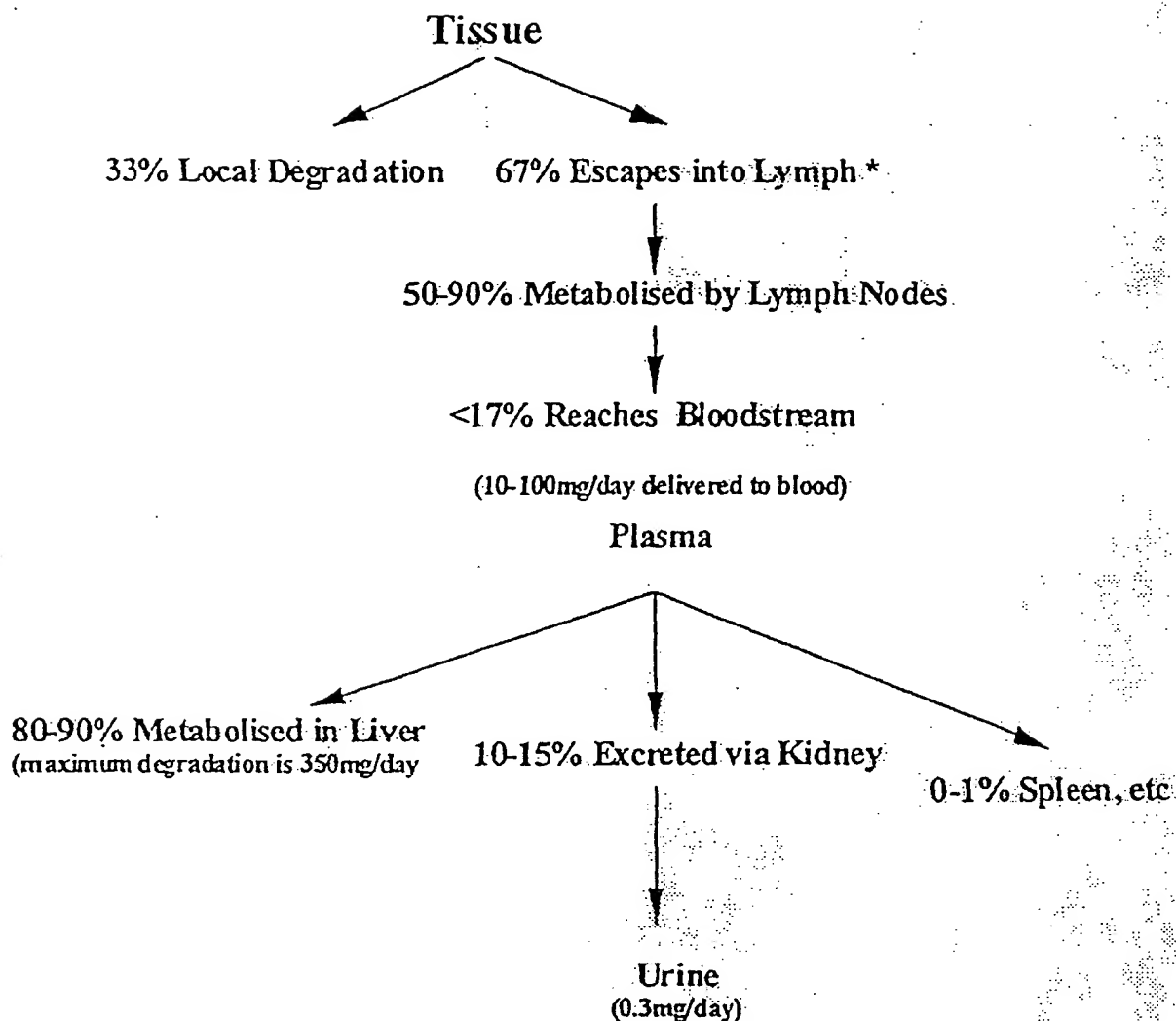
* Local catabolism will almost certainly dominate in very dense tissues, or those
without lymphatic drainage; for example, bone and cartilage

FIGURE 13

FIGURE 14

FIGURE 15

FIGURE 16

FIGURE 17

FIGURE 18

A

Lymph Node Involvement

*(Bar chart: Y-axis "% of Metastatic lymph nodes per animal" from 0 to 100. Bars labeled Saline (~93), 5-FU (~14) *, 5-FU/HA (~12) *, HA (~18) *. X-axis "Treatment Groups")*

B

New Tumour Formation

(Bar chart: Y-axis "Number of new tumours" from 0 to 4. Bars labeled Saline (3), 5-FU (1), HA/5-FU (arrow, 0), HA (arrow, 0). X-axis "Treatment Groups")
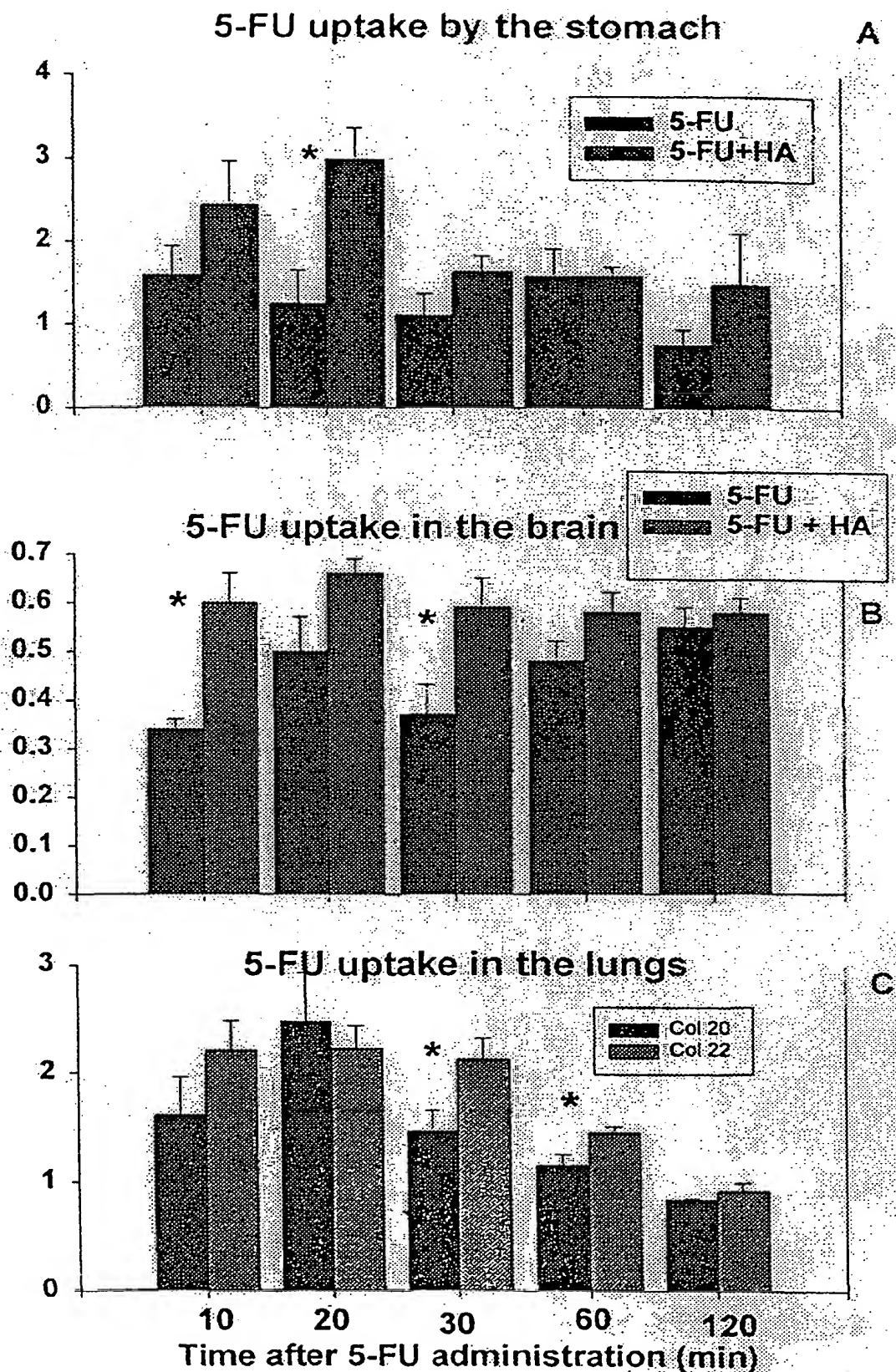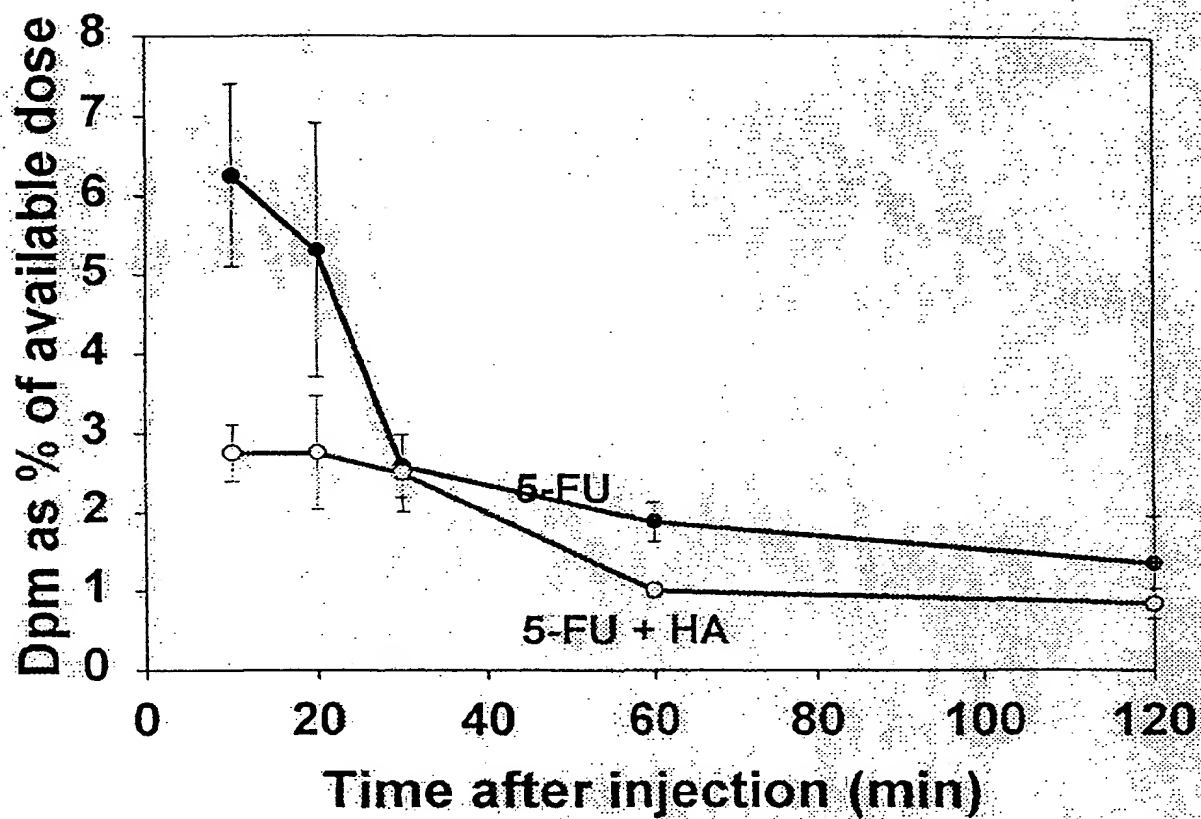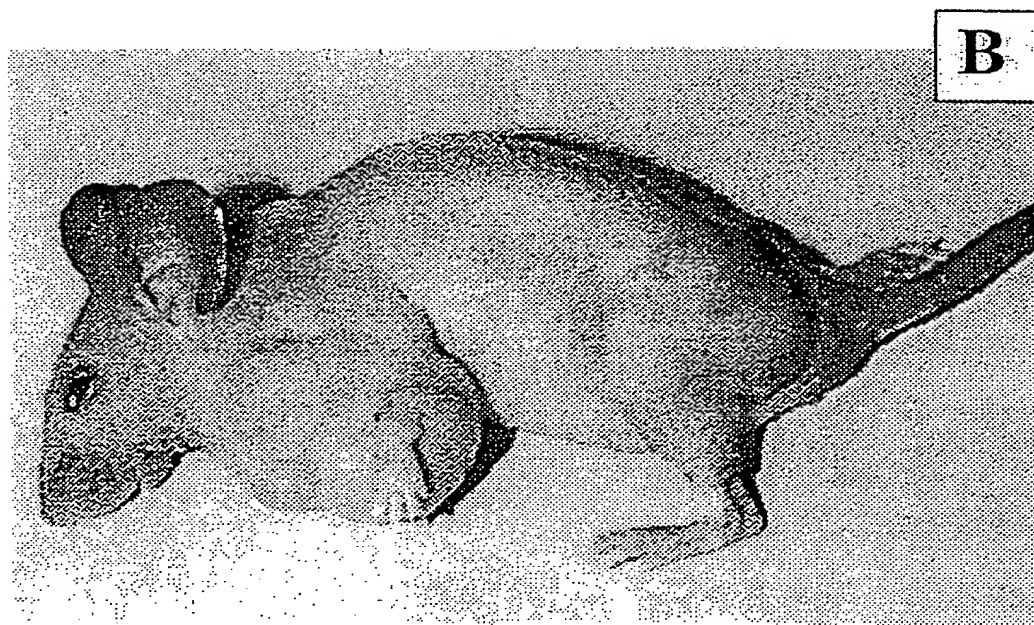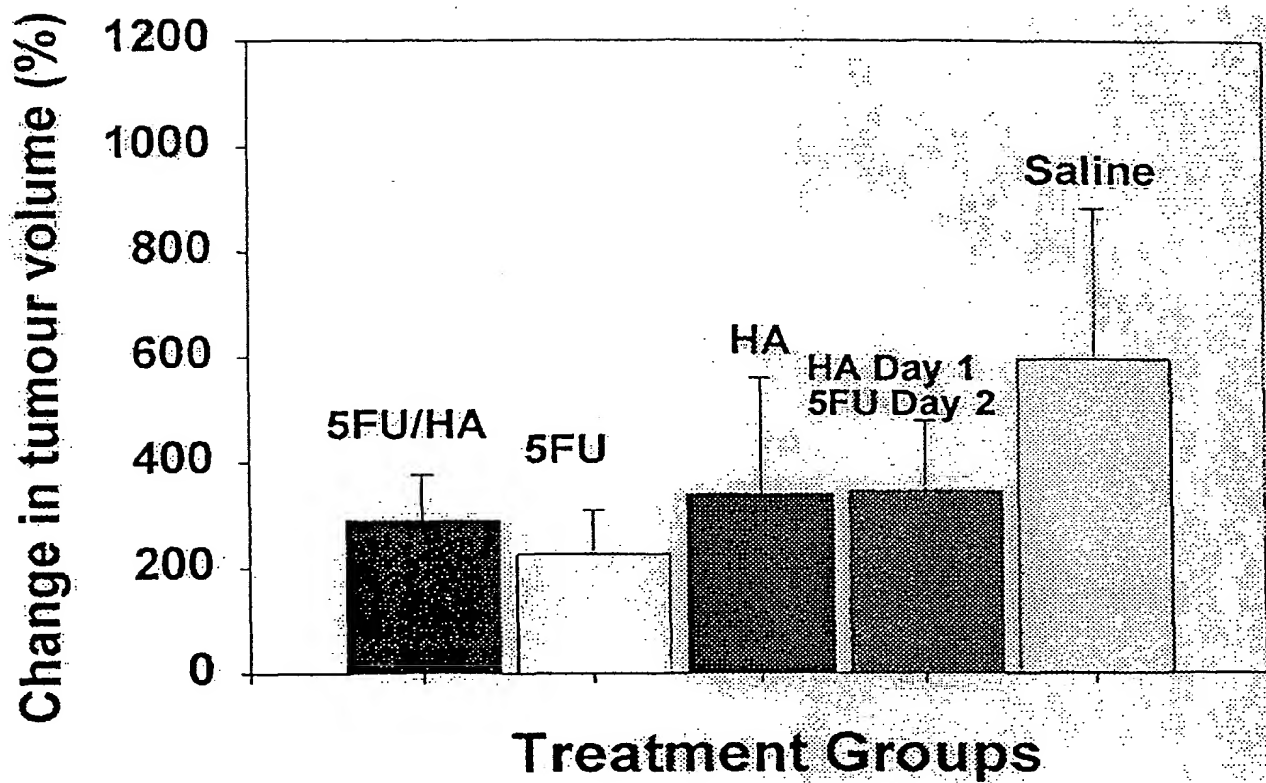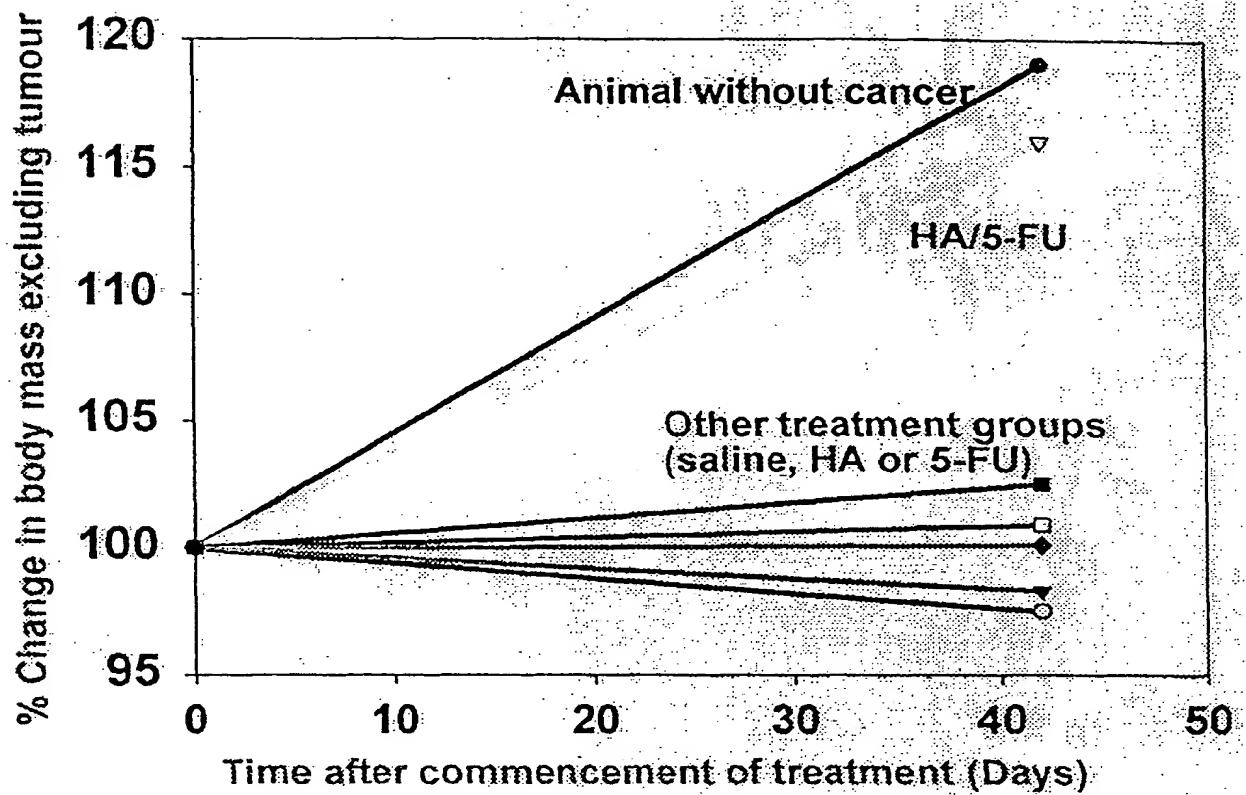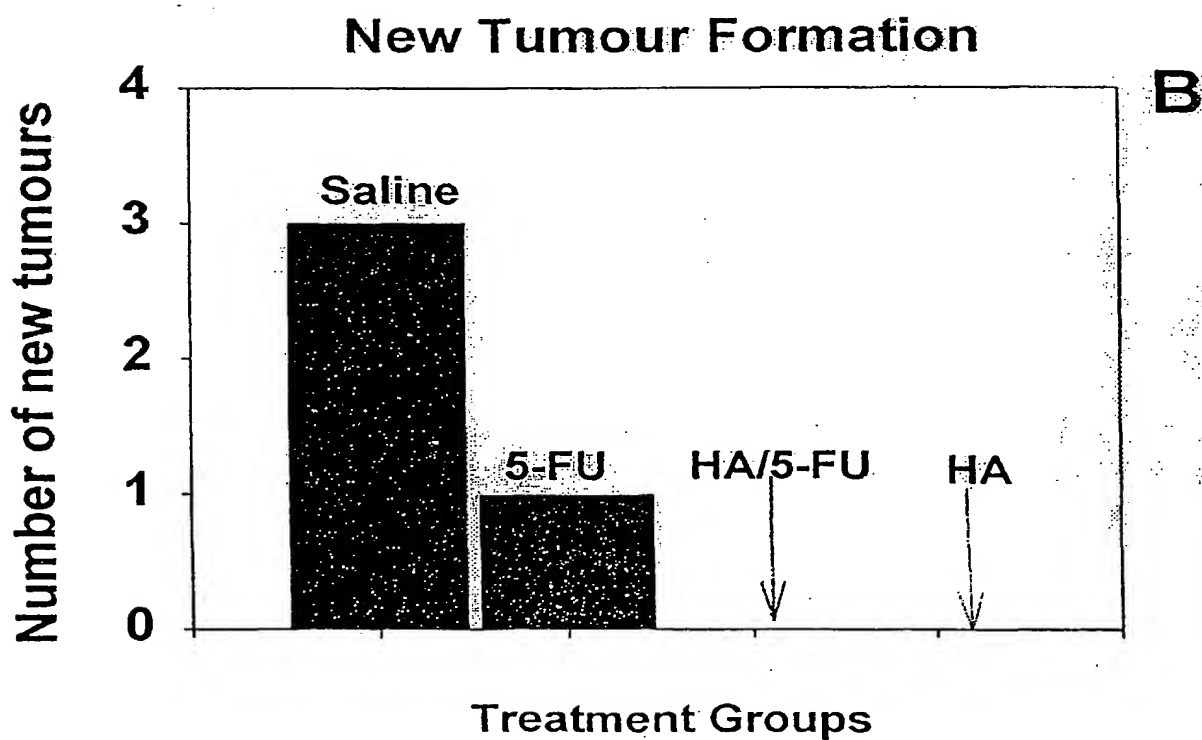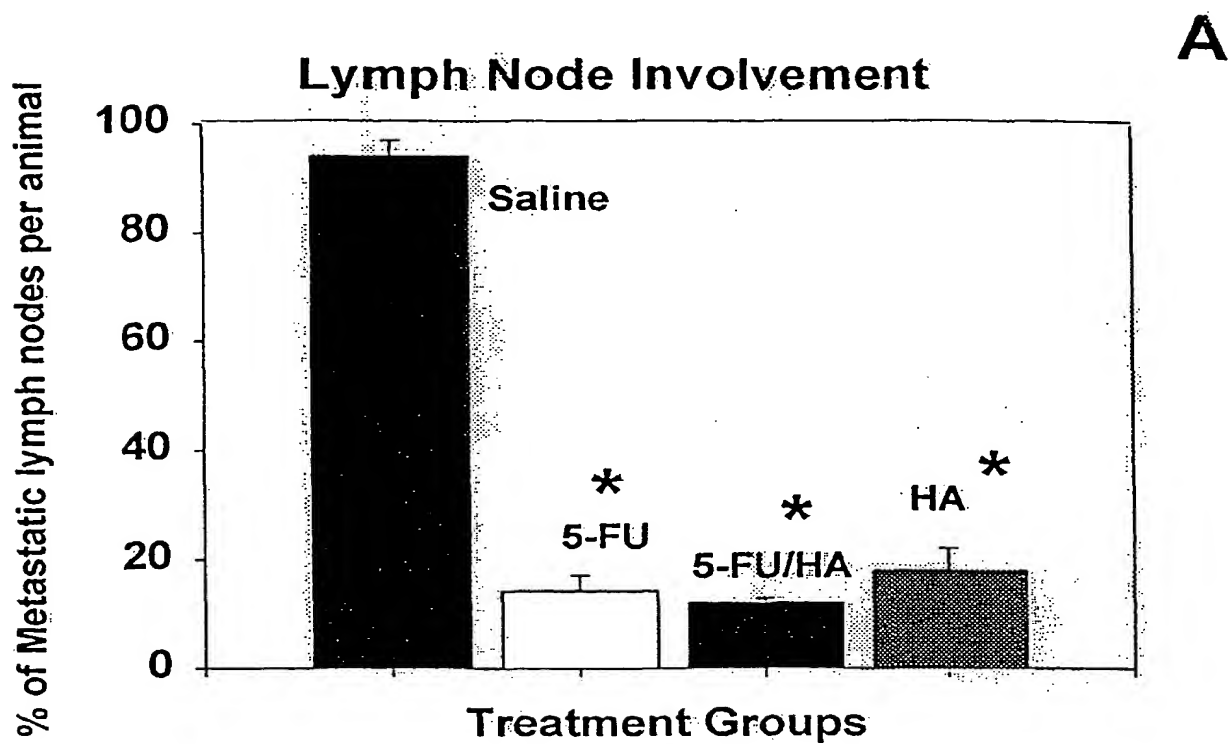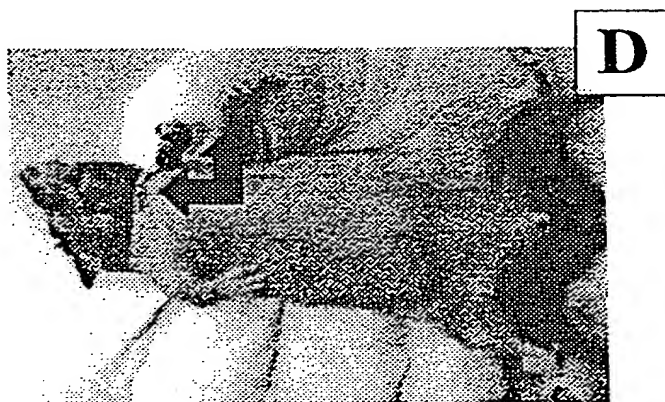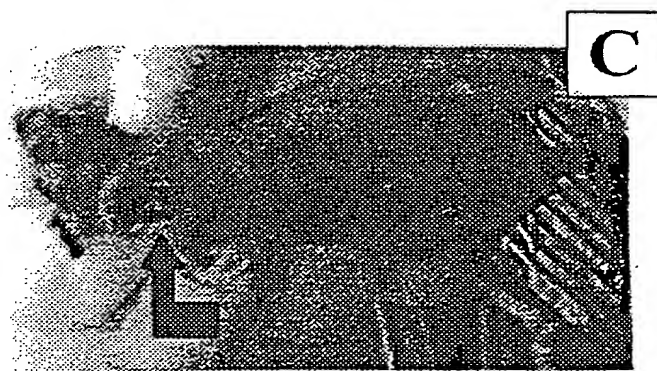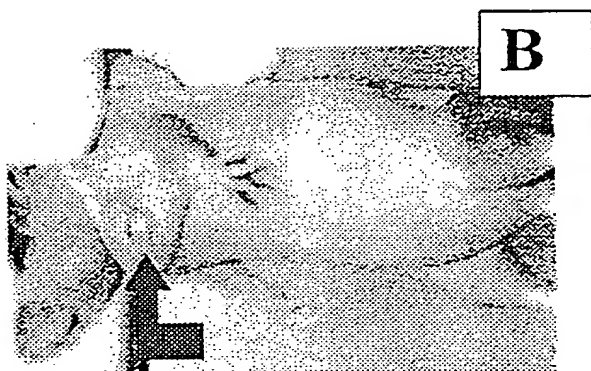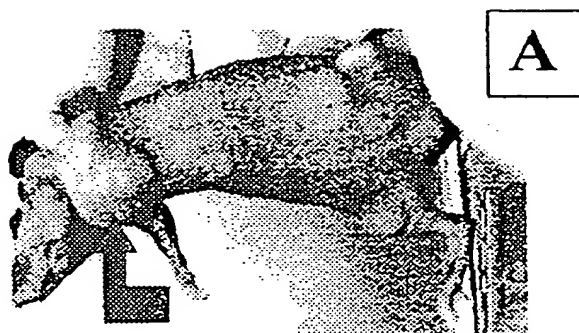
FIGURE 19
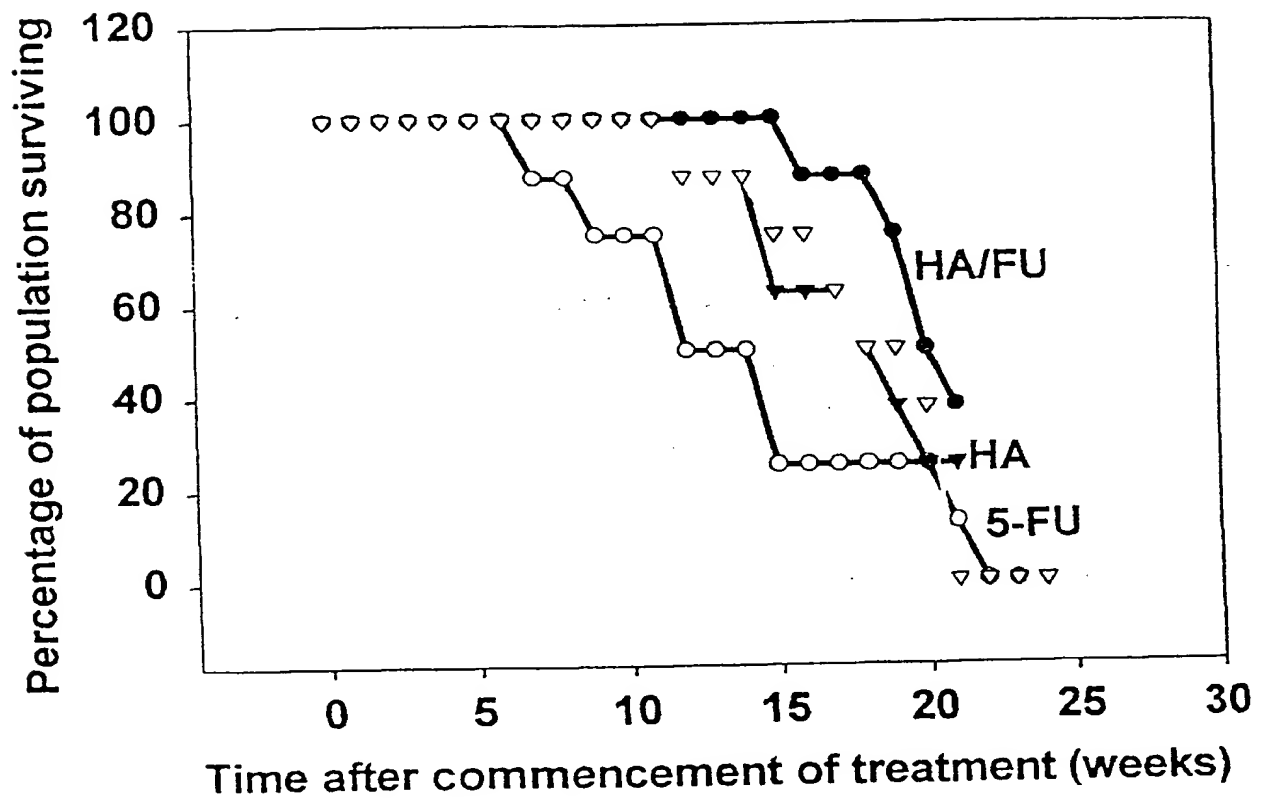
FIGURE 20

6 Month Study: Survival Curves

FIGURE 21
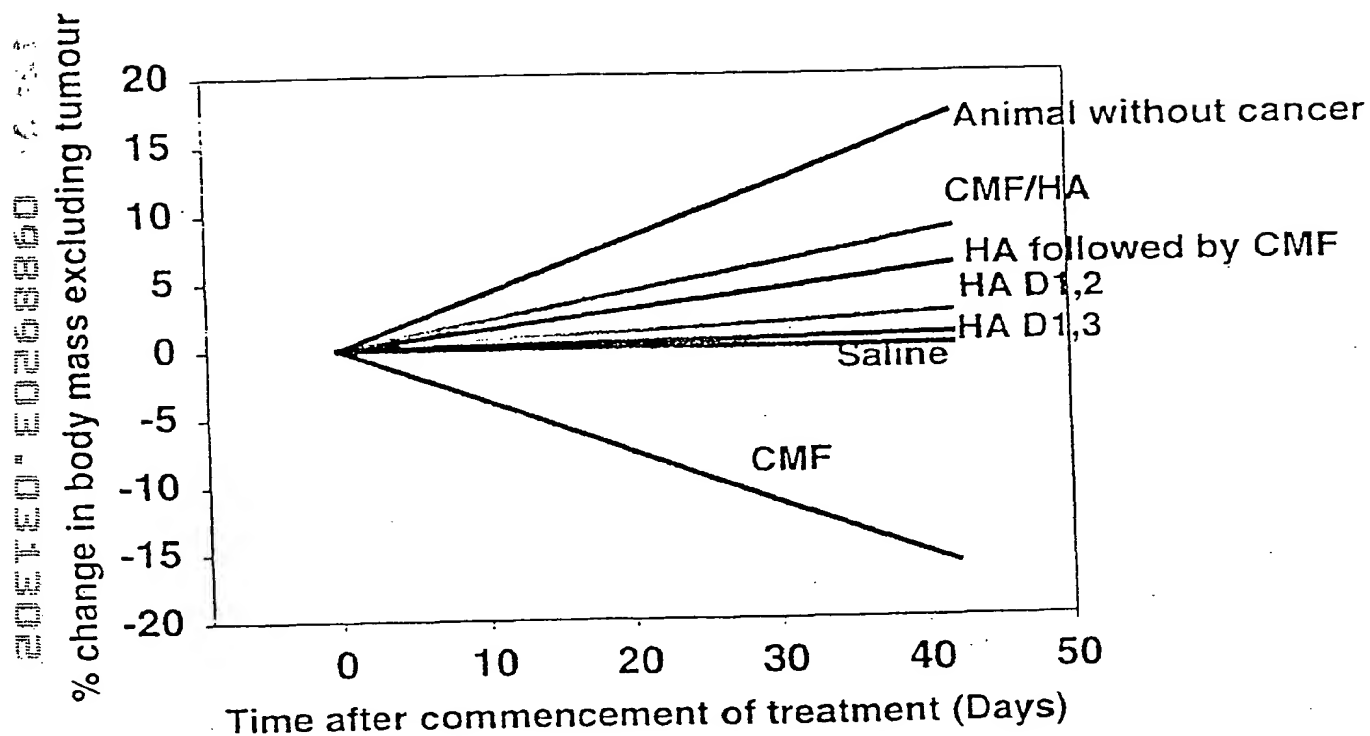
Effect of CMF/HA therapy on body mass:
6-week study

FIGURE 22

U9/889203

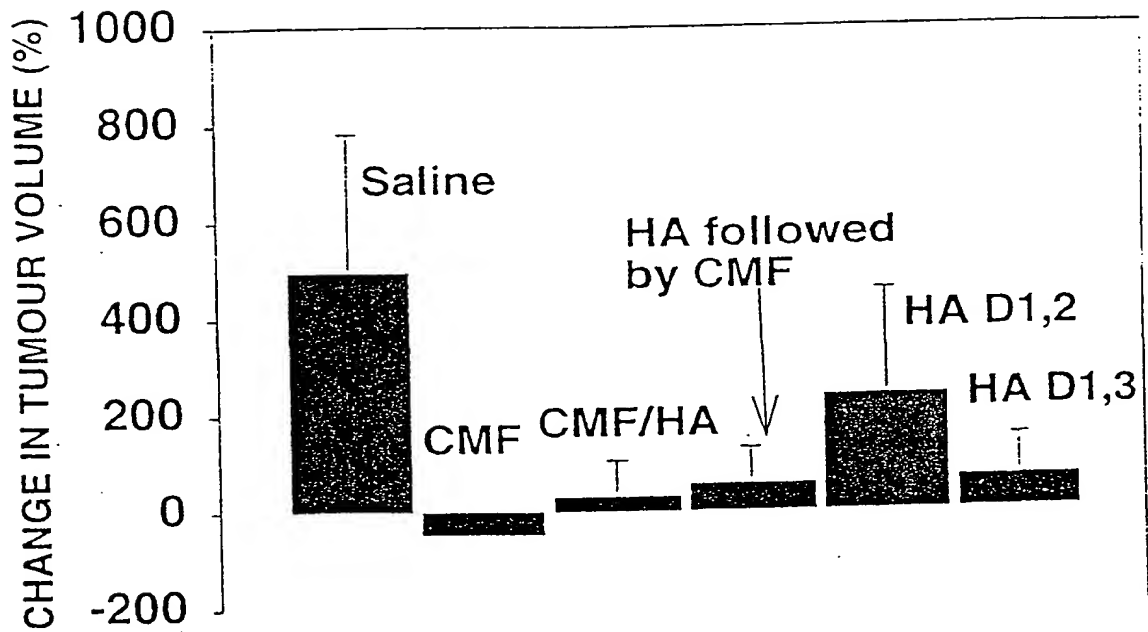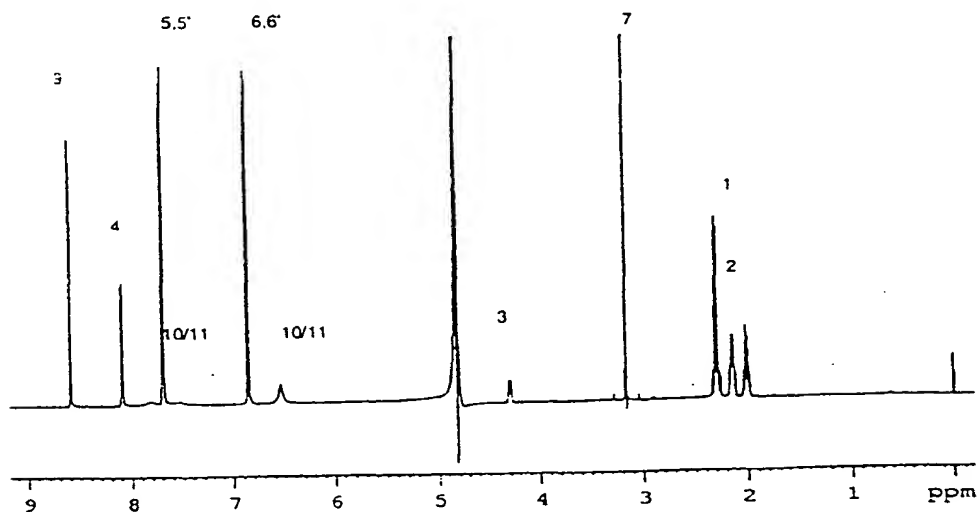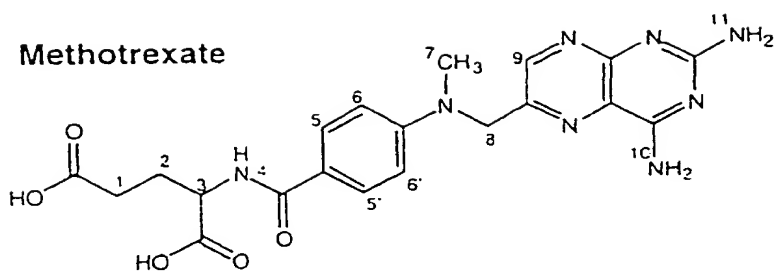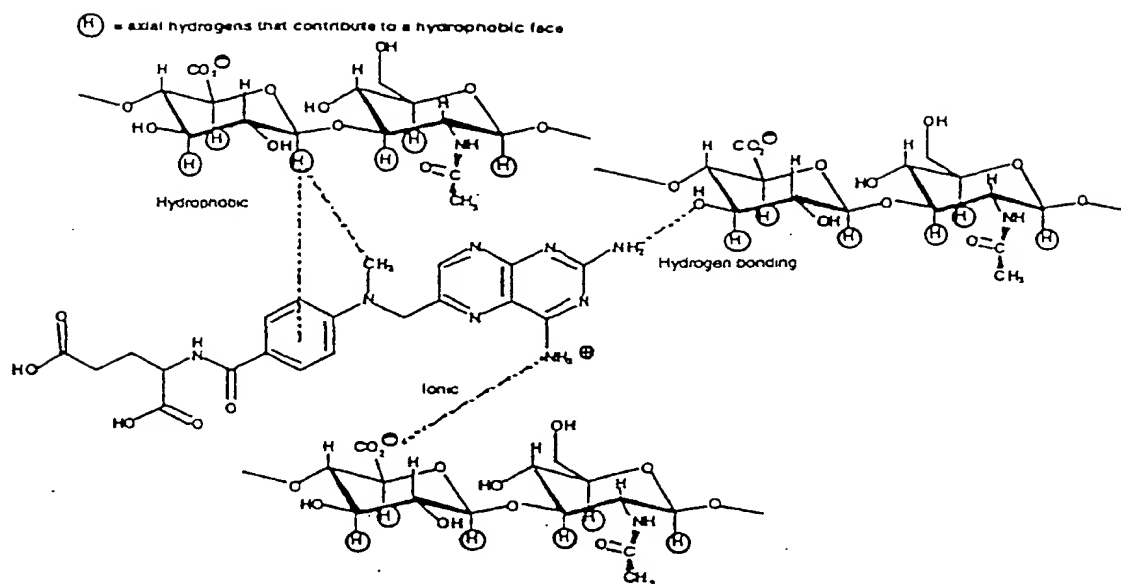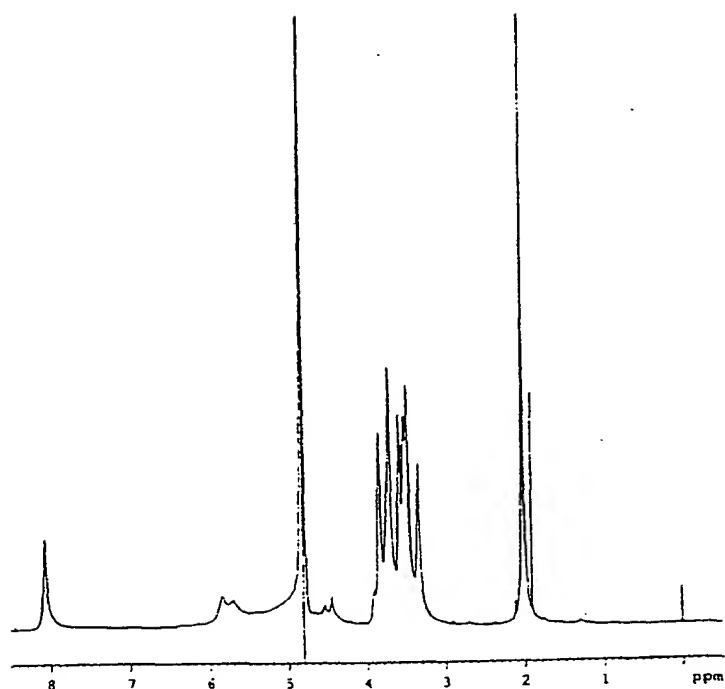Effect of CMF/HA adjuvant therapy on primary tumour mass

FIGURE 23

Methotrexate

FIGURE 24

FIGURE 25

FIGURE 26

FIGURE 27

FIGURE 28